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Report

Kinetics of Potassium Excretion Following Oral Supplements: Evidence of Induced Natriuresis

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Twenty-four healthy normal volunteers were given 40 mEq of three oral formulations of K^+ as potassium chloride in a three-way Latin square design. Pharmacokinetic characteristics of potassium disposition were determined using urinary excretion data. Potassium was absorbed almost instantaneously from the 10% (w/v) solution, while a slow first-order absorption could explain the slow release of potassium from Slow-K and the new slow-release tablet. A biphasic elimination of potassium observed during the first 24 hr of urinary excretion suggested the body's adaptive process of changes in rates of elimination of potassium to maintain homeostasis. There was no significant difference (P = 0.25) in total recoveries of potassium in urine during 48 hr of urinary collection among the three formulations (mean ± SE: solution, 35 ± 7.1 mEq; Slow-K, 38.1 ± 7.8 mEq; and new formulations, 33.5 ± 6.8 mEq). An increased excretion of sodium was observed and correlated with increased potassium excretion following oral potassium administration which could not be explained by changes in urine flow rate. The clinical significance of such an increase in natriuresis is yet to be determined.

KEY WORDS: potassium; absorption; excretion; induced natriuresis.

INTRODUCTION

Potassium, which is the principal intracellular cation, is essential for a number of physiological processes including nerve transmission, muscle contraction, and renal function. This cation also plays a key role in the genesis and correction of imbalances of acid–base metabolism.

Potassium supplementation is, therefore, necessary when depletion of this cation occurs. Such depletion usually develops slowly as a consequence of prolonged diuretic therapy, hyperaldosteronism, diabetic acidosis, severe diarrhea, or inadequate replacement in patients undergoing prolonged hyperalimentation. Oral dosage forms of potassium are, therefore, commonly used for supplementation. Potassium chloride (KCl) is the preferred salt for most situations, since chloride deficiency often coexists with that of potassium. Potassium supplementation has, however, been associated with a disturbing incidence of gastrointestinal side effects, primarily because of rapid disintegration of enteric-coated tablets (1–3). Localized release of high concentrations of potassium in the small intestine is now known to cause an unacceptably high incidence of gastrointestinal ulcerations (4,5). Hence, slow-release oral potassium supplements with a low incidence of gastrointestinal bleeding have found wide acceptance. One such product, Slow-K (Ciba-Geigy Corp., Summit, N.J.), has been available commercially for about a decade. This is a sugar-coated tablet in which KCl crystals are embedded in an insoluble wax matrix. Potassium gradually leaches out of the wax matrix. A new slow-release formulation, a membrane-coated tablet with a well-defined porous water-permeable diffusion membrane which is insoluble in the gastrointestinal tract, was evaluated for its release characteristics. The objective of this study was to determine the pharmacokinetics of potassium absorption and excretion after administration of the solution and the two slow-release formulations.

Urinary excretion of potassium is commonly used as a measure of *in vivo* absorption in humans. This is because of known resistance in plasma level changes of potassium following oral supplementation. Changes in urinary potassium excretion measurement are, however, much larger following oral supplements. Previous studies have demonstrated almost complete recovery of potassium in urine from solution and other slow-release dosage forms (6–9). In spite of several reports on the extent of bioavailability of potassium from oral potassium supplements, no information is available on the kinetics of potassium absorption and excretion.

In this study we examined (a) circadian variations in urinary potassium excretion on control days with a fixed diet, (b) pharmacokinetics of potassium absorption and excretion, and finally (c), the effect of oral potassium supplements on sodium excretion.

METHODS

Study Design

This was an open-label three-way Latin square-de-

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signed study in 24 normal healthy male volunteers balanced for residual effects. One of the following three drug doses was given to each subject on each of three separate occasions: (A) 30 ml of a 10% KCl solution (40 mEq of K^+) (potassium chloride oral solution U.S.P., Philips Roxane); (B) three 1-g new slow-release tablets (40 mEq); and (C) five 600-mg Slow-K tablets (40 mEq).

The sequence for the three dosage administrations to each subject was assigned randomly. The subjects were housed in a clinical study center and supervised continuously during their stay of 13 days. Each subject ate the same diet, consisting of 2400 cal and 50 and 100 mEq of potassium and sodium chlorides, respectively. The fluid intake for each 24-hr period was 1700 ml. Breakfast, lunch, dinner, and snack were served at 0900, 1330, 1700, and 2200 hr, respectively.

The standard diet and fluid intake were initiated 1 day before the treatment. On day 1, the subjects began the first of three 4-day identical treatment periods, except for the drug formulation. During the first and second day of each treatment period, the body was allowed to adapt to the diet and recover from the treatment given previously. Day 3 of each period served as the day for collecting control information (i.e., baseline urinary excretion and plasma concentrations of potassium). On day 4 of each period, the drug formulation was administered, following an 8-hr fast and 3 hr before breakfast. Day 5 (first day of the next treatment) was used to determine the amount of drug recovered during 24–48 hr of the earlier treatment.

Collection of Samples

Urine. On days 1, 2, 6, and 10, total 24-hr urinary excretion was recorded. On days 3 and 4 of each treatment period (i.e., days 3 and 4, 7 and 8, and 11 and 12), urine was collected hourly for 16 hr. The urine excreted during the remaining 8-hr interval (16–24 hr) was collected as a single specimen during the night. On days 5, 9, and 13, that is, the day following the first 24 hr of drug treatment, urine was collected at 4-hr intervals for the first 16 hr, followed by an 8-hr interval during the night.

Serum. Blood samples for serum electrolyte (K^+ and Na^+) determinations were collected at 0 (predose, 6:00 AM), 1, 3, and 6 hr on control and treatment days (days 3, 4, 7, 8, 11, and 12).

Analysis of Samples

Urine and plasma sodium and potassium were determined by flame-emission spectroscopy at emission wavelengths of 766.5 and 589.0 nm for potassium and sodium, respectively. An automated flame photometer (Model 480, Corning Medical and Scientific Instruments, Corning Glass Works, Medfield, Mass. 02052) with a built-in diluter was used.

Data Analysis

The net amount of potassium excreted over any time interval was calculated by subtracting the corresponding values obtained on control days from those obtained on treatment days. The first days of the three treatments were days 4, 8, and 12, while the corresponding control days were days 3, 7, and 11, respectively. Net excretion of potassium was calculated in a similar fashion for the second treatment day (days, 5, 9, and 13). The cumulative amount excreted over 0- to 24- and 0- to 48-hr periods was calculated by summation of the individual interval values. The cumulative net excretion of potassium over 0- to 24- and 0- to 48-hr intervals was analyzed by ANOVA.

RESULTS

The mean 24-hr total potassium excretion on 5 different control days (days 1, 2, 3, 7, and 11) was 41.9, 46.4, 44.1, 43.6, and 41.9 mEq, respectively. An analysis of variance showed no significant difference ($P > 0.05$) between subsequent control days. Hourly potassium excretions on control days 3, 7, and 11 were also compared to determine the diurnal variations in potassium excretion. An analysis of variance showed that the time of day influenced the urinary excretion of potassium (Fig. 1). Potassium excretion, as expected, increased after a meal was ingested. However, a comparison of corresponding hourly excretions on these 3 control days demonstrated no significant difference between days.

Mean excretions of potassium as milliequivalents (% dose) in 24 hr were 27.6 (69%), 28.1 (70%), and 23.1 (57%) for the solution, Slow-K, and new formulation, respectively. Analysis of variance showed no significant differences ($P = 0.111$) between formulations. Analysis of potassium excretion on the second day (days 5, 9, and 13) after treatment showed that it was significantly higher ($P = 0.0001$) than on control days (days 3, 7, and 11). Therefore, a significant amount of potassium was excreted from the formulation during the 24- to 48-hr interval after treatment. Net excretions of potassium during the 0- to 48-hr interval as milliequivalents (% dose) averaged 35.2 (88%), 37.9 (94%), and 34.0 (85%) for the solution, Slow-K, and new formulation, respectively. In this case also, the differences were not statistically significant ($P = 0.25$). Although a significant amount of potassium was excreted from the dosage form during the 24- to 48-hr interval collections, most of it was excreted during the first 24 hr (solution, 69 vs 88%; Slow-K, 70 vs 94%; and new formulation, 57 vs 85%).

Pharmacokinetic Model

The amount of potassium remaining to be excreted against time was fitted to different pharmacokinetic models using RS/1 (10) to determine the kinetics of potassium absorption and disposition. The calculated multi-r^2 of the regression and visual inspection of the fitted line were used to determine the goodness of fit. A two-exponential disposition function with bolus input was finally fitted to the urinary excretion data after the administration of potassium chloride solution, while a first-order input with a two-exponential disposition of potassium was fitted to the urinary potassium excretion data after both slow-release dosage forms (Fig. 2). Individual rate constants for three dosage forms are shown in Table I.

Influence on Sodium Excretion

Net excretions of potassium following three dosage forms were evaluated against net excretions of sodium (treatment–control) to determine any effect of potassium supplements on sodium excretion. Figure 3 depicts the mean

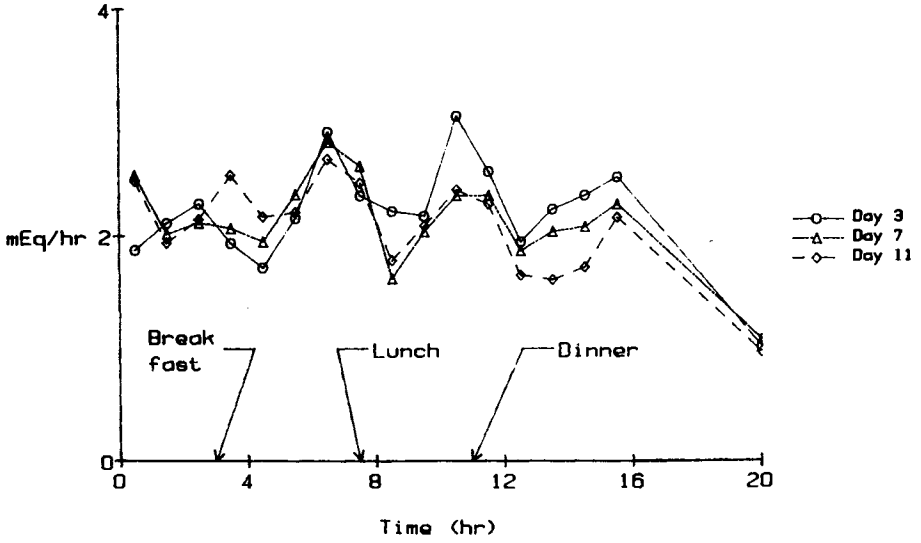

Fig. 1. Hourly potassium excretions on different control days.

net potassium excretion rates against the sodium excretion rates after the administration of solution in two representative subjects. Any effect of the urine flow rate on the observed correlations of sodium and potassium excretions was also evaluated as shown in Fig. 3 by simultaneous comparison of the flow rate with sodium excretion.

DISCUSSION

Absorption

Pharmacokinetic evaluation of potassium excretion from solution indicated a very rapid absorption in the gastrointestinal tract. Potassium absorption from two slow-release dosage forms was, however, much slower than from solution and could be described by a first-order (k_a) input rate (Table I, Fig. 2). In the presence of the rapid absorption of potassium from solution, these slower absorption rates from Slow-K (0.97 hr^{-1}) and the new formulation (0.35 hr^{-1}) reflect their slow release rates from the respective dosage forms. *In vitro* release data on new formulation indicated a comparable first-order release rate constant of 0.29 hr^{-1}.

Disposition

Very little information is available on the kinetics of dis-

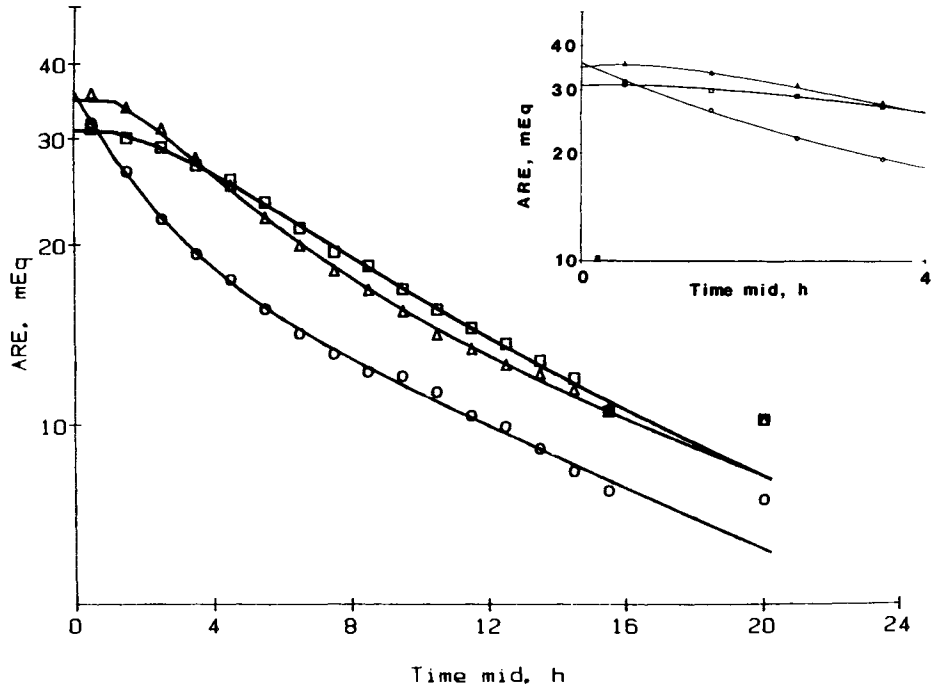

Fig. 2. Amount of potassium remaining to be excreted against time at midcollection interval. The solid lines represent the fitted curves calculated from the experimental data. (○) Solution; (△) Slow-K; (□) new formulation.

Table I. Pharmacokinetic Rate Constants (± SE) for Potassium Absorption and Disposition

	k_a (hr^{-1})	λ_1 (hr^{-1})	λ_2 (hr^{-1})
Solution	—	0.47	0.059
		(0.05)	(0.004)
Slow-K	0.97	0.26	0.049
	(1.10)	(0.19)	(0.038)
New formulation	0.35	0.26	0.057
	(0.19)	(0.21)	(0.034)

position of potassium when given as oral supplements. Fit of the potassium excretion data demonstrated a two-exponential disposition. One possible mechanism could be that these two exponents represent fast and slow phases of potassium elimination. Potassium being a predominant intracellular cation, kidney is known to adapt to changes in potassium load to maintain homeostasis. It is generally known that when the potassium intake is reduced, the amount of potassium excreted in the urine also decreases, but this is a gradual process and several days may be required to reduce the rate of excretion to the level of the rate of intake (11). Hyperkalemia also stimulates the secretion of glucagon, which has a hypokalemic effect through stimulation of the renal excretion of potassium (12). As seen in our study there is practically no change in the plasma level of potassium. Hence, the high excretion rate during early hours (1–6 hr) of potassium intake represents high plasma renal clearance followed by a decreased renal clearance during the late hours (6–16 hr) of urine collection. This adaptive response of the kidney seems to continue as seen by the even slower elimination rate during the 16- to 24-hr collection interval (Fig. 2), when still a significant amount of potassium was excreted from the dosage form as compared to that on the control day. The possibility of an extrarenal adaptation to increased potassium load, i.e., storage in muscle, liver, and red blood cells or a redistribution process, also cannot be excluded. Hyperkalemia is known to stimulate the release of insulin, which in turn facilitates cellular uptake of potassium. This redistribution process may not be reflected in plasma potassium concentration change because only 2.5% of exchangeable potassium is found in the extracellular fluid.

Whatever the mechanism may be of this multiexponential disposition of potassium, this still reflects the body's adaptive process of changes in rates of distribution and elimination of potassium to maintain a homeostasis.

The larger rate constant (λ_1) estimted for the three formulations is also greater for the solution compared to the two other slow-release dosage forms. This is in agreement with the adaptive hypothesis that solution with almost bolus input puts a greater load on the body compared to slow-release tablets and results in a higher renal clearance.

The two slow-release tablets, however, could not distinguish in their renal clearance values even with some difference in their release rates. The slower terminal phase (λ_2), as expected, demonstrated similar values for all three formulations.

Influence on Sodium Excretion

It is known that potassium being filtered freely at the glomerulus is about 90% reabsorbed from the tubular fluid by the time it reaches the distal tubule. The amount excreted in the urine normally gains access through a passive secretory process in the distal tubule down an electrochemical gradient. Any changes in the composition of the tubular fluid (e.g., Na^+ concentration, flow rate, etc.) favoring the electrochemical gradient may increase potassium secretion. It is not well known, however, whether the increased excretion of potassium observed following oral supplements has, in turn, any effect on sodium excretion.

After correcting the basal excretion for both Na^+ and K^+ by subtracting the excretion on control days (days 3, 7, and 11) from that on the potassium treatment days (days 4, 8, and 12), there appeared to be a positive correlation be-

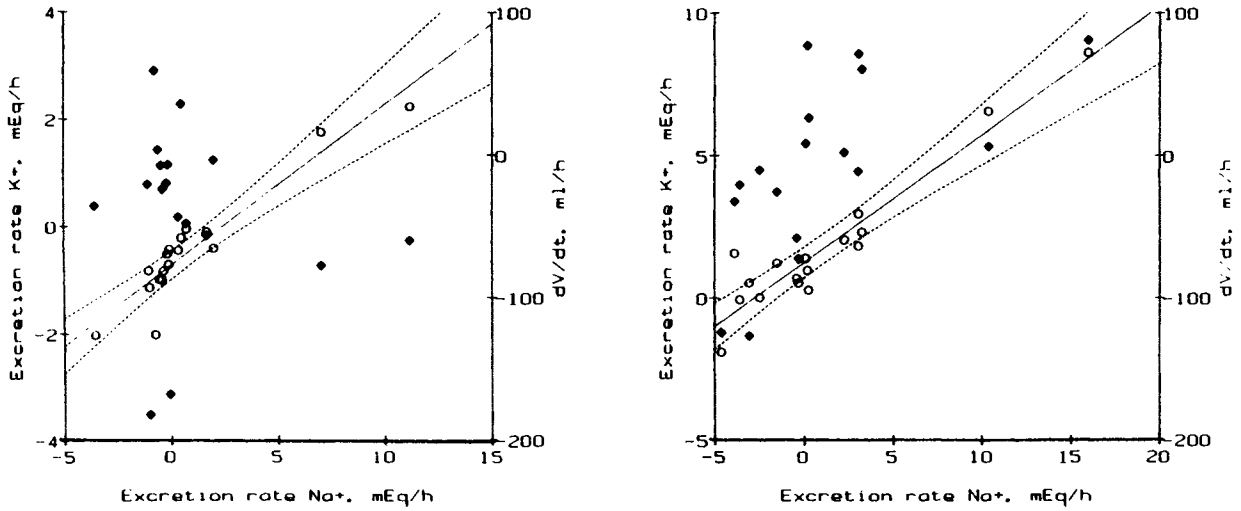

Fig. 3. Net excretion rates of potassium and urine flow rates (dV/dt) against sodium in two representative subjects (Nos. 1 and 3) after administration of solution. (○) Net excretion rate of potassium and (◆) changes in urine flow rate. The solid line represents the best-fitted regression line for excretion of potassium against that of sodium. The broken lines represent the 95% confidence interval around the mean regression line. The regression lines were $0.30 * x - 0.73$ for subject 1 and $0.45 * x + 1.23$ for subject 3.

tween potassium and sodium excretion (Fig. 3), with a Pearson correlation coefficient of 0.75 ($P = 0.0001$) for Slow-K, 0.72 ($P = 0.0001$) for the new formulation, and 0.64 ($P = 0.0001$) for the solution. It is also apparent (Fig. 3) that increased excretion of sodium observed following potassium administration cannot be explained by changes in urinary output. Such induced natriuresis may very well have added clinical benefit, especially when these oral potassium supplements are given to hypertensive patients on potassium-depleting diuretics. The clinical significance of such increased natriuresis, especially on chronic dosing, is yet to be determined.

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